RESPONSES BY THE STAFF OF THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT (OEHHA) TO COMMENTS ON THE APRIL 1994, DRAFT TECHNICAL SUPPORT DOCUMENT FOR USING CANCER POTENCY FACTORS (TSD)

Comments of Elizabeth H. Margosches, US EPA

1. Comment: "We would appreciate your comments on how the harmonization process could proceed further, particularly for those chemicals for which the Cal/EPA and US EPA unit risk values are essentially similar (for example, less than a two-fold difference)."

As indicated below for the short-chain chlorinated paraffins, often we're happy to round to the same order of magnitude. It seems that adopting a US EPA unit risk and accompanying it with a Cal/EPA discussion as well as the US EPA development may be a solution most likely to bring harmony not only with the US EPA figures but also with values that other states or risk assessment bodies may develop, since other bodies will also make comparisons to the US EPA unit risks. (Letter, dated June 13, 1997, pp. 1)

Response: Where appropriate, the post-public comment Technical Support Document for Describing Available Cancer Potency Values (TSD) has incorporated US EPA Integrated Risk Information System (IRIS) cancer potency values (See Preface, Hot Spots Unit Risk and Cancer Potency Values Table, Appendices E and F of the TSD). The remaining cancer potency values were adopted from the following Cal/EPA programs and documents: the Toxic Air Contaminant (TAC) program, the Proposition 65 program, and Maximum Contaminant Level water documents developed by the Pesticide and Environmental Toxicology Section for use by the Department of Health Services. These cancer potency values are also listed in the California Cancer Potency Factor List, which is published by the Office of Environmental Health Hazard Assessment (OEHHA). The hierarchy of choice listed in the Regulatory Agency Risk Assessment Methodologies of the TSD gave preference to sources which include external peer review and public comment procedures for publishing cancer potency values; this implements the Risk Assessment Advisory Committee (RAAC) recommendations that Cal/EPA risk assessment documents include provisions for external peer review and public comments. Additional weight of consideration was given to the most recent derivations using the latest data sets and scientific methodology. The publication procedure for Toxic Air Contaminant documents includes a public comment period and review by the Air Resources Board's Scientific Review Panel (SRP) before adoption by the Air Resources Board of the California Environmental Protection Agency (Cal/EPA). Furthermore, a petition procedure is available to initiate TAC document review and revision if required because of new or previously unconsidered toxicity data. The standard Proposition 65 document adoption procedure included a public comment and external peer review by the Proposition 65 Scientific Advisory Panel. The expedited Proposition 65 document adoption procedure includes a public comment period. Additionally, the cancer potency values developed by Cal/EPA are often newer than those developed by US EPA; in the case of most of the TAC document risk evaluations, a preexisting US EPA risk evaluation was acknowledged and taken into account during the preparation of those documents (see Appendix F of the TSD).

Some of the TAC documents also used data sets which were more recent that those used by US EPA in their corresponding risk assessment documents.

We believe that this document takes the first step in moving toward a comprehensive harmonization between the agencies by providing a clear listing of where the agencies differ. As indicated in the preface, revising Cal/EPA cancer unit risk and potency factors requires the original program to reconsider the value in an open public process. We would be happy to work with the appropriate component of US EPA to discuss the scientific issues surrounding the cancer unit risk values which are "essentially similar".

2. Comment: "As indicated above, the document proposes for adoption 12 US EPA IRIS cancer unit risk values. Currently, US EPA is considering revisions to its cancer risk assessment guidelines. Some of the proposed changes may modify the cancer unit risk values only slightly. We would appreciate your comments on whether we should automatically update these twelve specific US EPA cancer unit risk values if they are revised. For example, we anticipate that some changes in potency slopes and unit risk values will result from changing the body weight scaling factor from 2/3 to 3/4 power."

I believe once you choose to adopt US EPA IRIS cancer unit risk values, you must revise your values to match those the US EPA publishes. I would not think this would infringe on Cal/EPA's ability to make its decisions about when to use its values to update its regulations.

Response: Statute law (SB1082, Statutes of 1992, Calderon; SB1731, Statutes of 1994, Calderon) mandates that the approval process of new or revised documents produced by Office of Environmental Health Hazard Assessment (OEHHA), including the Air Toxics Hot Spots Risk Assessment Guidelines documents, incorporate external peer review by the SRP, and a public comment period including public workshops into that process. While use of this procedure would preclude an automatic revision of the US EPA IRIS cancer potency values incorporated in the TSD, it is our intent to closely follow the US EPA's process in revising its cancer risk assessment guidelines. If policy changes result in modifications in cancer unit risk values, it will be our responsibility to present the information in an open process to the Scientific Review Panel prior to approval.

3. Comment: pp. 7 & 8 **"Cancer Risk Assessment Methodologies**
United States Environmental Protection Agency (US EPA)

"US EPA carcinogen risk assessment procedures are generally described in Anderson *et al.* (1983) and "Guidelines for Carcinogen Risk Assessment" (US EPA, 1986), and are used in the calculation of cancer potency values listed on the Integrated Risk Information System (IRIS) (Office of Health and Environmental Assessment). US EPA states that cancer risk estimates based on adequate human epidemiologic data are preferred if available over estimates based on animal data.

"US EPA Calculation of Carcinogenic Potency Based on Animal Data

"The procedures used to extrapolate low-dose human cancer risk from animal carcinogenicity data generally assume that most agents that cause cancer also damage DNA, and that the quantal type of biological response characteristic of mutagenesis is associated with a linear non-threshold dose-response relationship. US EPA states that the risk assessments made with this model should be regarded as conservative, representing the most plausible upper limit for the risk. The mathematical expression used by US EPA to describe the linear non-threshold dose-response relationship at low doses is the linearized multistage model developed by Crump (1980). This model is capable of fitting almost any monotonically increasing dose-response data, and incorporates a procedure for estimating the largest possible linear slope at low extrapolated doses that is consistent with the data at all experimental dose levels.

"The linearized multistage model has the form

$P(d) = 1 - \exp[- (q_0 + a_1 d + q2d^2 + ... + qkd^k)]$, where $P(d)$ = lifetime risk (probability) of cancer at dose d, $q_i > 0$, and $i = 0, 1, 2, ..., k$. Equivalently, $A(d) = 1 - \exp [- (q_1 d + q_2 d^2 + ... + q_k d^k)]$, where $A(d) = (P(d) P(0))/(1 - P(0))$ *is* the extra risk over background at dose d. The point estimate of the coefficients q_i, $i = 0, 1, 2, ..., k$ and therefore the extra risk function A(d) at any given dose d, is calculated by maximizing the likelihood function of the data.

"US EPA uses updated versions of the computer program GLOBAL79 developed by Crump and Watson (1979) to calculate the point estimate and the 95% upper confidence limit of the extra risk $A(d)$. Upper 95% upper confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit q_1^* on a parameter q_1. When $q_1^* \neq 0$, at low doses the extra risk A(d) has approximately the form $A(d) = q_1^* * d$. This term is a 95% upper confidence limit on the extra risk and R / q_1^* is an approximate 95% lower confidence limit on the dose producing an extra risk of R. The upper limit of q_1^* is calculated by increasing q_1 to a value q_1^* such that when the log-likelihood is remaximized subject to this fixed value q_1^* for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation $2(L_0 - L_1) = 2.70554$, where L_0 is the maximum value of the log-likelihood function and 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, corresponding to a 95% upper limit (onesided). This method of calculating the upper confidence limit for the extra risk $A(d)$ *is* a modification of the Crump (1980) model. The upper confidence limit for the extra risk calculated at very low doses is always linear with dose. The slope q_1^* is taken as an upper bound of the potency of the chemical in inducing cancer at low doses.

"In fitting the dose-response model, the number of terms in the polynomial $g(d)$ equals $(h - 1)$, where h *is* the number of experimental dose groups (including the control group). If the model does not sufficiently fit the data, data from the highest dose are deleted and the model is refitted to the remaining data. This process is continued until an acceptable fit to the remaining data is accomplished. For purposes of determining if a fit is acceptable, the chi-square

$$x^2 = \sum_{i=1}^{h} \frac{(X_i - N_i P_i)^2}{N_i P_i (1 - P_i)}$$

is calculated, where N_i is the number of animals in the i_{th} dose group, x_i is the number of animals in the i_{th} dose group with a tumor response, P_i is the probability of a response in the i_{th} dose group estimated by fitting the multistage model to the data, and *h is* the number of remaining groups. The fit is unacceptable when chi-square (χ^2) is larger than the cumulative 99% point of the chi-square distribution with *f* degrees of freedom, where *f* is the number of dose groups minus the number of non-zero multistage coefficients."

The document isn't consistent in using "multistage" or "multi-stage".

Because the choice to use a bound on the linear term rather than the estimate of the curve itself is not actually a model, so much as a procedure, the algorithm described for deriving unit risks, etc., is properly called "linearized multistage procedure" and is so referenced in the 1986 US EPA Guidelines.

Since 1986, the US EPA has not been using the procedures quite as described in Anderson et *al.* (1983). GLOBAL86 entails a more complicated algorithm for polynomial g(d) = ln(l/(l-P(d))) selection than simply taking k = (h - 1); this is documented in a 1986 contract report available, I believe, from NCEA/ORD/US EPA. TOX_RISK may be used to obtain an equivalent set of coefficients by repeated application together with user tabulation and inspection. An example of text used to describe the GLOBAL86 algorithm is drawn from the 1987 Health Assessment Document on Acetaldehyde (p. 7-44ff):

'In fitting the dose-response model, the number of terms in the polynomial is chosen equal to k up to k = 6. The model with the value of k estimating the smallest upper-limit incremental unit risk and still providing an adequate (p > 0.01) fit to the data is retained and the corresponding q_1^* is employed.

'The point estimate, q_1^* and the 95% upper confidence limit of the extra risk $P_t(d)$ [denoted *A(d)* above] are calculated by using the computer program GLOBAL83, developed by Howe (1983, unpublished). At low doses, upper 95% confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit, q_1^*, on parameter q_1. Thus, the value q_1^* is taken as an upper bound of the potency of the chemical in inducing cancer at low doses...'

Response: The TSD has been revised to use the term "multistage" consistently and to use "multistage procedure" in place of "multistage model". The exact updated version of GLOBAL79 has been specified (GLOBAL86), and the description of the model algorithm has been changed to reflect the revisions contained in GLOBAL86.

4. Comment:

p. 14

"Adjustments are made for experimental exposure durations which are less than the lifetime of the test animal; the slope q_1^* is increased by the factor $(L/L_e)^3$, where L is the normal lifespan of the experimental animal and L_e is the duration of the experiment. This assumes that if the average dose *d is* continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. US EPA states that age-specific rates for humans increase by at least the 2nd power of the age, and often by a considerably higher power, leading to an expectation of an increase in the cumulative tumor rate, and therefore q_1^* to increase by at least the 3rd power of age. If the slope q_1^* is calculated at age L_e, it would be expected that if the experiment was continued for the full lifespan L at the same average dose, the slope q_1^* would have been increased by at least $(L/L_e)^3$."

One US EPA reference for this relationship to age is: P. Armitage and R. Doll, 1957, "A two-stage theory of carcinogenesis in relation to the age distribution of human cancer," Brit. Journal of Cancer 11: 161 ff.

Response: This section of the TSD has been revised to include a reference by Doll (Weibull distribution of cancer: implications for models of carcinogenesis, 1971, J Royal Stat Soc A, 13, 133-166), which is also cited by Anderson *et al*. (1983).

5. Comment: p. 12
"Unit risk factors $(\mu g/m^3)^{-1}$ are calculated from cancer potency factors $(mg/kg\text{-}day)^{-1}$ using the following relationship: UR = (CPF * 20 m^3)/(70 kg * CV), where UR is the unit risk, CPF is the cancer potency factor, 70 kg is the reference human body weight, 20 m^3 is the reference human inspiration rate/day, and CV is the conversion factor from mg to µg (= 1000)."

In 1989 US EPA's IRIS instituted the practice of presenting a slope factor for dietary intake use in $(mg/kg/day)^{-1}$, an oral unit risk (per µg/L), and an inhalation unit risk (per $\mu g/m^3$). This was done to remove the confusion that could occur 1) when a data set based on oral administration and one based on an inhalation study would provide differing slope factors, owing to the assumptions needed to convert the latter to the appropriate units and 2) when pharmacokinetic (PK) information was incorporated into inhalation concentration/dose conversions. Your text here does not appear to provide for the circumstance when inhalation data were the original source of the cancer potency factor and PK data were incorporated into its calculation, although individual chemicals acknowledge the possibility by distinguishing the inhalation unit risk from an oral cancer potency factor.

Response: The methodology discussion in this section describes the extrapolation of an inhalation unit risk factor from a cancer potency value calculated from oral exposure data. Four chemicals (methylene chloride, perchloroethylene, trichloroethylene and vinyl chloride) listed in the Unit Risk and Cancer Potency Values table included pharmacokinetic (PK) information in the calculation of their unit risk values. The metabolized fraction of the exposed dose of vinyl chloride was similar for both the ingestion and inhalation routes of administration. Use of PK modeling therefore would not be expected to make the inhalation

slope factor significantly different from the oral slope factor. The TSD was revised to include separate oral and inhalation cancer slope factors for methylene chloride, perchloroethylene and trichloroethylene. The oral slope factors were derived from oral exposure cancer studies, were developed by the Reproductive and Cancer Hazard Evaluation Section (RCHAS) for Proposition 65, and are listed in the California Cancer Potency Factors list.

6. Comment:
p. 18 Table
"Comparison of Hot Spots Cancer Unit Risk Values Which Differ From Corresponding US EPA IRIS Cancer Unit Risk Values"

The first case discussed in the document seems to be acetamide, and acetaldehyde does not seem to appear.

Response: A unit risk value for acetaldehyde is contained in the Hot Spots Unit Risk and Cancer Potencies table in the TSD. The unit risk value for acetaldehyde was developed in a separate Toxic Air Contaminant (TAC) document which has already undergone a public workshop, public comment period and an external scientific peer review process. Chemical-specific information summaries were not developed for chemicals for which TAC documents exist, as the documentation contained in the TAC document was considered sufficient for the purposes of the TSD. The TAC document contains an extensive discussion of the potential carcinogenicity of acetaldehyde. In our process of developing risk assessment documents, the Scientific Review Panel directed OEHHA to not bring approved chemical documents repeatedly for their review unless there had been an important change in the risk assessment analysis. For this reason, acetaldehyde is incorporated by reference in this document. TAC documents are listed in Appendix B.

7. Comment:
p. 88
"CHLORINATED PARAFFINS (Average chain length C12, 60% chlorine by weight)
CAS No: 108171-26-2...
II. HEALTH ASSESSMENT VALUES
Unit Risk Factor: 2.5 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 8.9 E-2 $(mg/kg\text{-}day)^{-1}$
[NTP (1986) female mouse liver tumor data, contained in Gold *et al.* database (1990), expedited Proposition 65 methodology (OEHHA, 1992), cross-route extrapolation.]"

Within our office, we calculated for CP-short chain (C-12): 0.1 per mg/kg/day (liver & thyroid tumors, female mice, benign & malignant, original NTP 1986 data), based on GLOBAL86 - contrast to short chain (C-12): 0.083 per mg/kg/day based on GLOBAL83 (This comparison is shown in a memo in our files from 8 Nov. 1991; such values cannot stand for the US EPA as a whole, but give you some idea of how the algorithms shift from GLOBAL83 to GLOBAL86.). Here's an instance, where values can be considered essentially similar (aside

from the difference in endpoint), as in your cover note's request for comment. Often numbers that round to the same order of magnitude are probably as good as you're going to get.

Response: The expedited Proposition 65 unit risk value for chlorinated paraffins was chosen because there was no corresponding unit risk value listed in IRIS. It is clearly consistent with the values provided by the commentor, although the commentor's cancer potency values are not listed on IRIS and do not represent US EPA as a whole. The commentor makes a good point that a number of minor differences between the agencies may be resolvable by rounding cancer unit risk and potency factors to a single significant digit.

8. Comment:
p.97
(p-chloro-o-toluidine hydrochloride): "3. Analysis of the data set using the computer program TOX_RISK (Crump et al., 1991) indicated that inclusion of the high dose group resulted in a *p*-value of ≥ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al.,* 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992)."

If you really have $p \sim 0.05$, you are NOT in the critical region, but in its complement; namely, you CANNOT REJECT the hypothesis that the data are linear. Is this a typo or did you make the wrong conclusion? You may wish to check other chemical summaries. Note, also, that the Anderson *et al.* (1983) procedure was not the dominant one for model **selection** at US EPA after 1986.

Response: The comment is correct; the statement "*p*-value of ≥ 0.05" should actually have read "*p*-value of ≤ 0.05". This and all other instances of this usage in the Chemical-Specific Information Summaries section of the TSD have been corrected. Additionally, the 1986 US EPA Guidelines for Carcinogen Risk Assessment have been referenced where appropriate.

9. Comment:
p. 165
"ETHYLENE THIOUREA (ETU) CAS No 96-45-7"

Is there a reason you did not use the F1 offspring of the 0-exposed F0 generation of the NTP 1992 feeding study in rats and mice (NTP Technical Report No. 388)? Two positive doses plus control would be available.

Response: No new cancer unit risk or potency values were developed for the TSD; all values listed here were previously developed by either Cal/EPA or US EPA. The expedited Proposition 65 cancer potency value listed in the TSD was calculated prior to the availability of the above mentioned NTP report. This information will be passed on to the Proposition 65 program for their review.

10. Comment: p.246
"POLYCHLORINATED BIPHENYLS (PCBs) (a 60% chlorine content) CAS No: 1336-36-3 (all congeners)"

This section does not seem to have taken into account Brunner et al. (1996) and the September 1996 US EPA "PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures", available at http:/www.epa.gov/ORD/WebPubs.

Response: The TSD has been revised to incorporate the cancer unit risk and potency values for polychlorinated biphenyls from the corresponding US EPA IRIS 1996 listing.

11. Comment: p. 260
"PROPYLENE OXIDE, CAS No: 75-56-9; II. HEALTH ASSESSMENT VALUES
Unit Risk Factor: 3.7 E-6 $(\mu g/m^3)^{-1}$ [Calculated by US EPA (1995) from male rat nasal cavity hemangioma/hemangiosarcoma data (NTP,1985) using a linearized multistage procedure, extra risk.]
Oral Cancer Potency Factor: 2.4 E-1 $(mg/kg/day)^{-1}$ [Calculated by US EPA (1995) from female Sprague-Dawley rat forestomach squamous cell carcinoma tumor data (Dunkelberg, 1981), using a linearized multistage model, extra risk.]"

In one line, the reference to "linearized multistage procedure" is correctly made; in the other, the word "model" is incorrectly used!

Response: The TSD has been revised to use the term "multistage" consistently and to use "multistage procedure" in place of "multistage model".

12. Comment:
p. 262
"US EPA has stated that the unit risk should not be used if the air concentration exceeds 3 mg/m^3, since above this concentration the unit risk may not be appropriate."

This kind of caveat is associated with all the unit risks and slope factors taken from IRIS, but it does not seem to appear in all the Cal/EPA summaries based on IRIS. It is suitable for **any** approximation that presumes linearity at low doses, since mere multiplication of such a figure times an exposure or dose cannot accommodate the levelling off in cumulative risk at high exposures/doses.

Response: The Chemical-Specific Information Summaries section of the TSD has been revised to include this information where appropriate.

13. Comment: p. 310

"APPENDIX D: Asbestos Quantity Conversion Factors: The unit risk factor for asbestos is listed in this document in units of 100 PCM fibers/m^3 [1.9 E-4 (100 PCM fibers/m^3)$^{-1}$] and in units of µg/m^3 [6.3 E-2 (µg/m^3)$^{-1}$]. The value listed in the Toxic Air Contaminant (TAC) document for asbestos (CDHS, 1986) was 1.9 E-4 (100 PCM fibers/m^3)$^{-1}$.... Use of the unit risk factor listed in the asbestos TAC document [1.9 E-4 (100 PCM fibers/m^3)$^{-1}$], wherever possible, will result in a more precise risk estimation. Additionally, the unit risk factor expressed in units of (µg/m^3)$^{-1}$ may change if a conversion factor with less uncertainty is developed, or may be eliminated if asbestos quantity reporting requirements render use of a unit risk factor expressed in units of (µg/m^3)$^{-1}$ unnecessary.

California Department of Health Services (CDHS) 1986. Report to the Air Resources Board on Asbestos. Part B. Health Effects of Asbestos. Epidemiological Studies Section, Berkeley, CA.

U.S. Environmental Protection Agency (US EPA) 1985. Airborne Asbestos Health Assessment Update. EPA/600/8-84/003F, Office of Health and Environmental Assessment, Washington, DC.

The US EPA citation should be designated 1986. This document, dated June 1986, has also been peer reviewed, and is the 1987 source of the IRIS value. Since, unlike, say, acrylonitrile, no summary is given for the development of the California unit risk, it's hard to tell what generated the divergence in the numbers. Additional explanation seems warranted.

Response: Appendix D of the TSD has been revised to include the correct date of the US EPA reference. The unit risk value for asbestos was developed in a Toxic Air Contaminant (TAC) document. Chemical-specific information summaries were not developed for chemicals for which TAC documents exist, as the documentation contained in the TAC document was considered sufficient for the purposes of the TSD. TAC documents are listed in Appendix B.

14. Comment: p. 311 "APPENDIX E: US EPA IRIS INHALATION UNIT RISK AND ORAL CANCER POTENCY FACTORS FOR CHEMICALS LISTED IN THE TSD".

The oral potency factor column needs an exponent to denote the reciprocal.

Response: Appendix E of the TSD has been revised to include the above listed omission.

Comments of the Chemical Manufacturers Association

1. Comment: The Olefins Panel of the Chemical Manufacturers Association (CMA) is pleased to present the following comments on the Office of Environmental Health Hazard Assessment's (OEHHA) proposed cancer potency factor for 1 ,3-butadiene. The proposed cancer potency factor will be used in California's Air Toxics "Hot Spots" Program, which requires affected facilities to conduct risk assessments of their air releases.

The cancer potency factor proposed for butadiene relies on the same data used by OEHHA in 1992 when it proposed to identify butadiene as a Toxic Air Contaminant, and indeed, is identical to the cancer potency factor derived in that documents OEHHA based its assessment of the butadiene cancer risk on two studies in mice, the most sensitive species. (Butadiene is significantly less potent in the rat than in the mouse.) In developing its "best value" unit risk for butadiene, OEHHA relied on the highly conservative assumptions that are part of its generic risk assessment methodology, rather than on current knowledge of the metabolism and mechanism of action of butadiene in the mouse, rat, monkey and man.

The Panel believes that the 1992 document does not present an accurate and balanced assessment of the health risks from exposure to butadiene, and that OEHHA's proposed cancer potency factor overstates the actual human risk from exposure to butadiene, particularly at low ambient concentrations. OEHHA has not addressed the comments submitted by the Panel on its 1992 health assessment of butadiene, and has not considered the many scientific developments since 1992 that have helped to elucidate both the mechanism of action of butadiene and the relevance of the mouse data for predicting human health effects. The Panel urges OEHHA to consider these data and to revise its cancer potency factor for butadiene accordingly.

In its comments on OEHHA's 1992 health assessment, the Panel described why the mouse is uniquely sensitive to the carcinogenic effects of butadiene, and therefore should not be used to estimate human health risks. (A copy of these comments is provided at Attachment 1.) The Panel therefore recommended that the range of risk estimates presented by OEHHA be expanded to make use of the available data on species differences in butadiene metabolism and mechanism of action. These comments further explained that because mice metabolize butadiene differently from rats and humans, OEHHA's "best value" risk estimate should be based on the rat bioassay. Similarly, any butadiene risk assessment should use the available butadiene-specific metabolism data to determine an appropriate scaling factor for animal-to-human extrapolation. The Panel also recommended that OEHHA acknowledge in its health assessment that human health risk estimates based on the mouse data are inconsistent with the epidemiology studies for butadiene taken as a whole.

Data developed since 1992 confirm that the mouse provides an inappropriate model for human health risk assessment, significantly overstating potential risks. For example, subsequent research has shown that the substantial differences in butadiene metabolic activation between rats and mice likely is responsible for the differential toxic effects seen in these two species. Specifically, mice produce 40 to 100 times more of the diepoxide

metabolite of butadiene than rats. This diepoxide metabolite, however, has been found to be 100 times more mutagenic than the monoepoxide. On the basis of *in vitro* data, however, it is expected that levels of the diepoxide metabolite would be even lower in humans than in rats. Accordingly, the relative body burden in humans of the diepoxide is expected to be orders of magnitude lower than in mice. These data confirm that any risk assessment should be based on the rat bioassay, and should use butadiene-specific metabolism data to identify an appropriate scaling factor for animal-to-human extrapolation.

The University of Alabama recently published an epidemiology study reporting an slight increase in the incidence of leukemia in the styrene-butadiene rubber industry. The slight increase in leukemia incidence in this study is inconsistent with a cancer potency factor derived from the mouse studies, and particularly does not support the use of such a potency factor to estimate human cancer risks at the very low levels associated with ambient exposure levels.

The Olefins Panel continues to sponsor an extensive and ongoing research program. Begun in 1991, this program has focused on developing an understanding of the basis for the apparent species differences in response to butadiene so that meaningful estimations of human health risks can be made. As described above, the studies conducted to date have shown that, because of profound species differences in butadiene metabolism, the mouse model does not appear to be relevant for human quantitative risk assessment. The Panel currently is expanding its previously-developed physiologically-based pharmacokinetic model to predict metabolite levels in humans, conducting further assessments of the animal cancer studies, and developing dose-response models for risk assessments. Other groups are sponsoring research on other aspects of butadiene toxicity, such as the causes of the dominant lethal and teratogenic effects in mice and their relevance to humans, butadiene mutagenicity and the differences in toxic responses to varying exposure levels (e.g., continuous low doses versus short-term peak exposures) of butadiene. (An overview of this research program is provided at Attachment 4.) This comprehensive, integrated research program is expected to expand significantly the already extensive body of evidence relating to species differences in butadiene metabolism and mechanism of action.

In conclusion, the Panel urges OEHHA to reevaluate its proposed cancer potency factor for butadiene to reflect the significant developments in the understanding of butadiene toxicity that have occurred over the past six years. In particular, the Panel believes that in developing its cancer potency factor, OEHHA should not rely on the mouse carcinogenicity studies. Rather, OEHHA should use the rat bioassay. Moreover, regardless of the species selected, the available butadiene-specific metabolism data should be used to identify an appropriate scaling factor for animal-to-human extrapolation.

Response: No new cancer unit risks or potency values were developed for the TSD. The cancer unit risk and potency values for 1,3-butadiene were developed as part of a Toxic Air Contaminant (TAC) document. The appropriate venue for reconsideration of cancer potency values developed as part of a TAC document would be the Air Resources Board (ARB). Appendix G of the TSD describes the procedure for submitting new scientific information to

the ARB pertaining to TAC risk assessments. The information supplied by the Chemical Manufacturers Association has been forwarded to the ARB for consideration.